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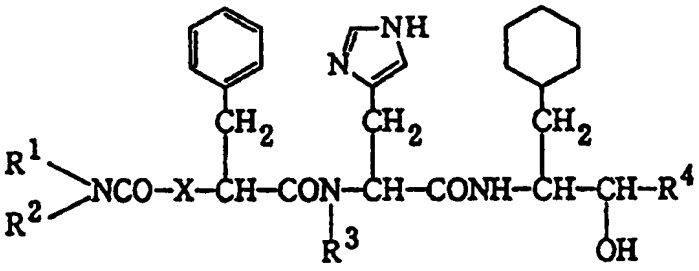
(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING RENIN INHIBITORS

(57) Abstract

This invention relates to an oral pharmaceutical composition characterized by comprising an amino acid derivative of general formula (I) wherein each symbol is as defined in the description, or a salt thereof and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.



(I)

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DESCRIPTION

ORAL PHARMACEUTICAL COMPOSITIONS CONTAINING RENIN INHIBITORS

Technical Field

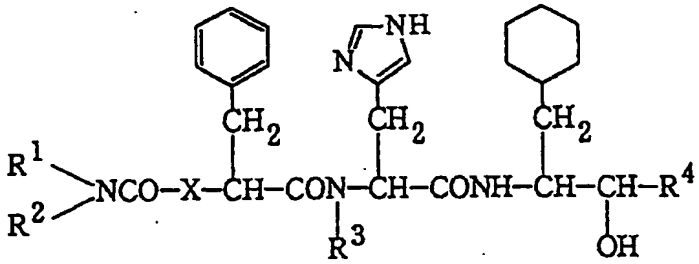
This invention relates to an oral pharmaceutical composition comprising a compound of general formula (I) given below or a salt thereof, which has renin-inhibitory activity, and more particularly to an oral pharmaceutical composition comprising said compound (I) or a salt thereof and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

Accordingly, one object of this invention is to provide an oral pharmaceutical composition comprising said compound (I) or a salt thereof and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

Further, another object of this invention is to provide a process for preparing an oral pharmaceutical composition comprising said compound (I) or a salt thereof and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

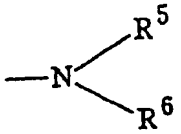
Background Art

A compound of general formula (I) :



(I)

wherein R^1 is a lower alkyl group which may be substituted with a substituent selected from the group consisting of acyl, hydroxy, lower alkoxy, aryl, lower alkylthio and a group of the formula :



in which R^5 is hydrogen or an acyl group, and R^6 is hydrogen or a lower alkyl group,

R^2 is hydrogen or a lower alkyl group,

R^3 is hydrogen or a lower alkyl group,

R^4 is a lower alkyl group, and

X is O or NH,

or a salt thereof is known to be a substance having renin-inhibitory activity (cf. Japanese Patent Application Publication Nos. 19071/1988, 243674/1990, 279570/1992) and is expected to find application in the field of medicine as a therapeutic drug for hypertension, heart failure, etc..

For any renin inhibitors, the development of oral dosage forms is considered desirable in view of the above-mentioned indications but many of renin inhibitors reported so far are poorly absorbed from the gastrointestinal tract and this has been a major deterrent to the development of oral dosage forms. For the above compound (I) or salt thereof [hereinafter referred to collectively as compound (I)], too,

attempts have been made to develop them as renin inhibitors for oral administration but a further improvement is needed in oral absorbability.

The inventors of this invention did much research for enhancing the oral absorption of compound (I) and found that tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and/or polyglycerin ester of fatty acid contributes a great deal to improved absorbability of compound (I) after oral administration. They accordingly have completed this invention.

Disclosure of the Invention

The oral pharmaceutical composition of this invention is characterized in that it comprises an active ingredient comprising compound (I) and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

The definitions used in general formula (I) and relevant specific examples as well as preferred working modes are explained in detail below.

The term "lower" means a group having 1 - 7 carbon atoms unless otherwise indicated.

Suitable "lower alkyl" includes straight-chain or branched alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, ethylbutyl, pentyl, isopentyl, hexyl, methylhexyl, heptyl or the like.

Suitable "aryl" includes phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl or the like, and the more preferred one is phenyl.

Suitable "lower alkoxy" includes a straight-chain

or branched alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, and the more preferred ones are C_1-C_4 alkoxy groups.

Suitable "acyl" includes lower alkanoyl groups such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, 4-methylvaleryl, etc., mono- or di(lower)alkylamino(lower)alkanoyl groups such as methylaminoacetyl, methylaminopropionyl, dimethylaminobutyryl, etc., lower alkoxy(lower)alkanoyl groups such as methoxyacetyl, methoxypropionyl, ethoxypropionyl, etc., aroyl groups such as benzoyl, toluoyl, etc., cyclo(lower)alkylcarbonyl groups such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentyl-carbonyl, cyclohexylcarbonyl, etc., amino acid residues whose amino groups may be protected, such as glycyl, benzoylglycyl, tert-butoxycarbonylglycyl, tert-butoxycarbonylleucyl, acetylleucyl, tert-butoxy-carbonylhistidyl, etc., carbamoyl, mono- or di(lower)-alkylcarbamoyl groups such as methylcarbamoyl, ethyl-carbamoyl, propylcarbamoyl, isopropylcarbamoyl, butyl-carbamoyl, pentylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, methylethylcarbamoyl, methylisopropylcarbamoyl, methyl-isobutylcarbamoyl, etc., heterocyclic(lower)alkyl-carbamoyl groups such as picolylcarbamoyl, pyridyl-ethylcarbamoyl, thiazolylmethylcarbamoyl, morpholino-methylcarbamoyl, morpholinoethylcarbamoyl, etc., N-heterocyclic(lower)alkyl-N-lower alkylcarbamoyl groups such as N-picolyl-N-methylcarbamoyl, N-pyridylethyl-N-methylcarbamoyl, N-morpholinomethyl-N-ethylcarbamoyl, N-morpholinoethyl-N-methyl-carbamoyl, etc., ar(lower)alkylcarbamoyl groups such as benzylcarbamoyl, phenethylcarbamoyl, benzhydrylcarbamoyl, etc., N-ar(lower)alkyl-N-lower alkylcarbamoyl groups such as N-

benzyl-N-methylcarbamoyl, N-phenethyl-N-methylcarbamoyl, N-phenethyl-N-ethylcarbamoyl, etc., N-aryl-N-lower alkylcarbamoyl groups such as N-phenyl-N-methylcarbamoyl etc., lower alkoxycarbonyl(lower)alkylcarbamoyl groups such as methoxycarbonylmethylcarbamoyl, ethoxycarbonylmethylcarbamoyl, ethoxycarbonylethylcarbamoyl, etc., lower alkoxy(lower)alkylcarbamoyl groups such as methoxymethylcarbamoyl, methoxyethylcarbamoyl, ethoxypropylcarbamoyl, etc., aroylcarbamoyl groups such as benzoylcarbamoyl, toluoylcarbamoyl, etc., heterocycliccarbamoyl groups such as pyridylcarbamoyl, morpholinocarbamoyl, thiazolylcarbamoyl, etc., N-heterocyclic-N-lower alkylcarbamoyl groups such as N-pyridyl-N-methylcarbamoyl, N-thiazolyl-N-methylcarbamoyl, etc., heterocycliccarbonyl groups and more preferably N-containing heterocyclic-N-ylcarbonyl groups which may be substituted with lower alkyl, such as morpholinocarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, 4-methyl-1-piperazinylcarbonyl, 1,2,3,6-tetrahydro-1-pyridylcarbonyl, etc., lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc., mono-(or di- or tri-)halo(lower)alkoxycarbonyl groups such as iodoethoxycarbonyl, dichloroethoxycarbonyl, trichloroethoxycarbonyl, trifluoromethoxycarbonyl, etc., hydroxy(lower)alkoxycarbonyl groups such as hydroxymethoxycarbonyl, hydroxyethoxycarbonyl, hydroxypropoxycarbonyl, hydroxybutoxycarbonyl, etc., ar(lower)alkoxycarbonyl groups such as benzyloxycarbonyl, phenethyloxycarbonyl, 4-nitrobenzyloxycarbonyl, trityloxycarbonyl, benzhydryloxycarbonyl, etc., lower alkenyloxycarbonyl groups such as vinyloxycarbonyl, allyloxycarbonyl, etc., lower alkanoyl(lower)alkoxy-

carbonyl groups such as acetylmethoxycarbonyl, propionylmethoxycarbonyl, acetylethoxycarbonyl, etc., lower alkylsulfonyl groups such as mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc., arylsulfonyl groups such as phenylsulfonyl, tosyl, etc. or the like.

Suitable "lower alkylthio" includes straight-chain or branched alkylthio groups such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, pentylthio, hexylthio or the like. The more preferred ones are C_1-C_4 alkylthio groups.

Suitable salts of compound (I) include conventional non-toxic salts, for example, organic acid addition salts such as formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc., inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, etc., salts with amino acids, such as aspartate, glutamate, etc. or the like.

Compound (I) may occur as stereoisomers, such as optical isomers and geometrical isomers, due to the asymmetric carbon and double bond and these isomers are also included within the scope of this invention.

Higher alcohol used in this invention includes C_8-C_{20}, straight-chain or branched, saturated or unsaturated alcohol such as cetyl alcohol, stearyl alcohol, oleyl alcohol or the like, in which more preferred ones are C_{14}-C_{20} alcohol and the most preferred one is cetyl alcohol.

Cyclodextrin used in this invention includes α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, γ-cyclodextrin, dimethyl-β-cyclodextrin

or the like, in which the most preferred one is β-cyclodextrin.

Sucrose ester of fatty acid used in this invention includes sucrose ester of mono-, di-, tri- or poly-, saturated or unsaturated fatty acid such as sucrose ester of lauric acid, sucrose ester of myristic acid, sucrose ester of palmitic acid, sucrose ester of stearic acid, sucrose ester of oleic acid, etc., and mixture thereof, sucrose ester of hardening beef tallow fatty acid [e.g. DK ester F-160, DK ester SS (manufactured by Dai-ichi Kogyo-Seiyaku Co., Ltd.)] or the like.

Polyglycerin ester of fatty acid used in this invention includes decaglycerin ester of fatty acid such as decaglycerin ester of monolauric acid [e.g. Decaglyn 1-L (trademark, manufactured by Nikko Chemicals Co., Ltd.)], decaglycerin ester of monostearic acid, etc. or the like.

The amount of tartaric acid or citric acid in the oral pharmaceutical composition of this invention is not so critical but is preferably 0.01 - 20 times and, for still better results 0.1 - 2 times, most preferably 0.5-1 times the amount of compound (I) contained in the composition.

The amount of higher alcohol in the oral pharmaceutical composition of this invention is not so critical but is preferably 0.05 - 20 times and, for still better results 0.1 - 10 times, most preferably 0.2-4 times the amount of compound (I) contained in the composition.

The amount of cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid in the oral pharmaceutical composition of this invention is not so critical but is preferably 0.5 - 20 times and, for still better results, 0.5 - 3 times the amount of

compound (I) contained in the composition.

Where necessary, the composition of this invention may further contain those additives which are conventionally used in pharmaceutical formulation, such as a disintegrator, lubricant, excipient, coloring agent, effervescent agent or the like. There is no limitation on dosage form. Thus, for oral administration, the composition can be used in such forms as powders, fine granules, granules, capsules, tablets, pills, liquid preparations, or the like.

Suitable disintegrator includes starches (e.g. potato starch, corn starch, hydroxypropylstarch, carboxymethylstarch sodium, etc.), cellulose derivatives (e.g. carboxymethylcellulose calcium, carboxymethylcellulose sodium, carboxymethylcellulose, low-substitution hydroxypropylcellulose, crystalline cellulose, etc.), polyvinylpyrrolidone, croscarmellose sodium or the like. Suitable lubricant includes talc, waxes (e.g. bleached beeswax, hydrogenated oil, etc.), stearic acid compounds (e.g. stearic acid, magnesium stearate, calcium stearate, etc.) or the like. Suitable excipient includes sugars (e.g. lactose, sucrose, D-mannitol, etc.), starches (e.g. corn starch etc.), inorganic salts of calcium (e.g. calcium hydrogen phosphate, calcium sulfate, etc.) or the like. Suitable coloring agent includes yellow oxide of ion, tar dyes or the like. Suitable effervescent agent includes a tartaric acid-sodium hydrogen carbonate system or the like. These are not exclusive choices, however, and any materials that are commonly used in the art can be utilized.

Where desired, the composition can be processed into a dosage form such as one coated with an enteric coating agent such as hydroxypropylmethylcellulose phthalate.

Furthermore, the tartaric acid or citric acid in this invention can be expected to double as a release enhancing agent.

The composition of this invention can be produced by blending compound (I) with one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid, and, optionally, further with conventional additives.

The method of production includes the conventional procedures. Moreover, such compositions as mentioned above can be comminuted for reducing the particle size. Such comminution can be made by the conventional procedures.

The powdery mixture so produced can be further processed, if desired, into various dosage forms by the processes well established in the art, such as pulverization, sieving, kneading, granulation, compression, coating or the like. These processes can each be carried out in the conventional manner.

In case that cyclodextrin is contained in the composition of this invention, an inclusion compound of compound (I) and cyclodextrin may be formed, and said inclusion compound is also included within the scope of this invention.

Some representative test data are given below for showing the effect of the invention.

Test compounds

(2S,3S)-2-[N^{α}-[(S)-2-[N-Methyl-N-[2-{N-(morpholinocarbonyl)-N-methylamino}ethyl]aminocarbonyloxy]-3-phenylpropionyl]-N^{α}-methyl-L-histidyl]amino-1-cyclohexyl-3-hydroxy-6-methylheptane hydrochloride

(hereinafter referred to Compound A)

(2S,3S)-2-[N^{α}-[(S)-2-{N-(2-Morpholinocarbonylethyl)-N-methylaminocarbonyloxy}-3-phenylpropionyl]-N^{α}-methyl-L-histidyl]amino-1-cyclohexyl-3-hydroxy-6-methylheptane hydrochloride

(hereinafter referred to Compound B)

Test 1 Solubility test

Method

An aqueous solution of the test compound (2 ml, concentration: 20 mg/ml, about pH 4) was prepared and maintained at 37°C. A solution of β-cyclodextrin, DK ester SS or Decaglyn 1-L in two-fold salt concentration of Second Fluid of The Pharmacopoeia of Japan (2 ml, concentration: 10 mg/ml, pH 6.8) was added thereto. The solubility of the test compound was determined by high performance liquid chromatography.

Results

Additives		β-cyclo-dextrin	DK ester SS	Decaglyn 1-L	none
Solubility (mg/ml)	Compound A	4.7	3.4	2.1	0.1
	Compound B	1.9	5.6*	1.9*	0.3

* a solution of two-fold concentration of Second Fluid of The Pharmacopoeia of Japan concentration: 20 mg/ml

It is apparent from the above test results that the solubility of the compound (I) is greatly improved by cyclodextrin, sucrose ester of fatty acid or polyglycerin ester of fatty acid.

Test 2 Oral absorption test-1

Method

Male S.D. rats (body weights 200 - 270 g), fasted overnight, were used in groups of 3. The dosing samples shown below were respectively administered orally to the rats in the dose of 10 mg/kg. After the administration, the blood was serially withdrawn from the femoral artery and the concentration of the test compound was determined by high performance liquid chromatography.

Dosing sample

Formulation	Formulation 1	Control
Compound A	20 mg	20 mg
β-cyclodextrin	46 mg	-
Purified water	10. ml	10 ml

Results

The test results are shown below in the table. The maximum plasma concentration (Cmax, μg/ml) and the area under the plasma concentration-time curve (AUC_{0-6} hr, μg•hr/ml) are shown together as oral absorption parameters. Each value is the mean ± standard error.

Formulation	n	Cmax (μg/ml)	$AUC_{0-6\ hr}$ (μg•hr/ml)
1	3	1.02±0.15	0.95 ± 0.17
Control	3	0.80±0.10	0.56 ± 0.07

Test 3 Oral absorption test-2

Method

Male S.D. rats (body weights 200 - 270 g), fasted overnight, were used in groups of 3. The dosing samples shown below were respectively administered orally to the rats in the dose of 32 mg/kg. After the administration, the blood was serially withdrawn from the femoral artery and the concentration of the test compound was determined by high performance liquid chromatography.

Dosing sample

Formulation	Formulation 2	Control
Compound A	64 mg	64 mg
Tartaric acid	32 mg	-
Purified water	10 ml	10 ml

Results

Formulation	n	Cmax (μg/ml)	$AUC_{0-6\ hr}$ (μg•hr/ml)
2	3	0.40±0.08	1.38 ± 0.30
Control	3	0.21±0.64	0.64 ± 0.13

Test 4 Oral absorption test-3

Method

The test was carried out according to a similar manner to that of Test 3.

Dosing sample

Formulation	Formulation 3	Control
Compound A	64 mg	64 mg
Cetyl alcohol	128 mg	-
Sorbitan sesqui-oleate (surfactant)	12.8 mg	12.8 mg
Purified water	10 ml	10 ml

Results

Formulation	n	Cmax (μg/ml)	$AUC_{0-6\ hr}$ (μg•hr/ml)
3	3	0.70±0.15	1.45 ± 0.41
Control	3	0.24±0.05	0.88 ± 0.12

It is apparent from the above test results that the oral pharmaceutical composition of this invention is superior to the cyclodextrin-free control composition, the tartaric acid-free control composition or the higher alcohol-free control composition in the oral absorbability of compound (I).

Examples

The following examples are intended to describe this invention in further detail.

Example 1

Compound A	200 parts
β-Cyclodextrin	465 parts
Crystalline cellulose	20 parts
Tartaric acid	185 parts
Sodium hydrogen carbonate	210 parts
Crosslinked polyvinylpyrrolidone	10 parts
Magnesium stearate	25 parts
Hydroxypropylmethylcellulose 2910	30 parts
Hydroxypropylmethylcellulose phthalate 220824	50 parts

Effervescent enteric tablets according to the above formula were manufactured by the conventional

method.

Example 2

Compound B	200 parts
DK ester SS	400 parts
Crystalline cellulose	20 parts
Tartaric acid	185 parts
Sodium hydrogen carbonate	210 parts
Crosslinked polyvinylpyrrolidone	10 parts
Magnesium stearate	25 parts
Hydroxypropylmethylcellulose 2910	30 parts
Hydroxypropylmethylcellulose phthalate 220824	50 parts

Effervescent enteric tablets according to the above formulation were manufactured by the conventional method.

Example 3

Compound A	200 parts
Decaglyn 1-L	400 parts
Crystalline cellulose	20 parts
Tartaric acid	185 parts
Sodium hydrogen carbonate	210 parts
Crosslinked polyvinylpyrrolidone	10 parts
Magnesium stearate	25 parts

Effervescent tablets according to the above formulation were manufactured by the conventional method.

Example 4

Compound A	600 parts
Lactose	45 parts
d-Tartaric acid	300 parts
Hydrous silicon dioxide	80 parts

Crosslinked polyvinylpyrrolidone	270 parts
Magnesium stearate	54 parts

Tablets according to the above formula were manufactured by the conventional method.

Example 5

Compound A	600 parts
Lactose	195 parts
Citric acid	150 parts
Hydrous silicon dioxide	80 parts
Crosslinked polyvinylpyrrolidone	270 parts
Magnesium stearate	54 parts

Tablets according to the above formulation were manufactured by the conventional method.

Example 6

Compound A	400 parts
Cetyl alcohol	400 parts
Lactose	105 parts
Crosslinked polyvinylpyrrolidone	80 parts
Magnesium stearate	15 parts

Tablets according to the above formula were manufactured by the conventional method.

Example 7

(2S,3S)-2-[N^{α}-[N-[N-Methyl-N-{2-(N-morpholino-carbonyl-N-methylamino)ethyl}aminocarbonyl]-L-phenylalanyl]-N^{α}-methyl-L-histidyl]amino-1-cyclohexyl-3-hydroxy-5-ethylheptane hydrochloride (hereinafter referred to Compound C)

	200 parts
β-Cyclodextrin	465 parts
Crystalline cellulose	20 parts
Tartaric acid	185 parts
Sodium hydrogen carbonate	210 parts

Crosslinked polyvinylpyrrolidone	10 parts
Magnesium stearate	25 parts
Hydroxypropylmethylcellulose 2910	30 parts
Hydroxypropylmethylcellulose phthalate 220824	50 parts

Effervescent enteric tablets according to the above formula were manufactured by the conventional method.

Example 8

Compound C	600 parts
Lactose	45 parts
d-Tartaric acid	300 parts
Hydrous silicon dioxide	80 parts
Crosslinked polyvinylpyrrolidone	270 parts
Magnesium stearate	54 parts

Tablets according to the above formula were manufactured by the conventional method.

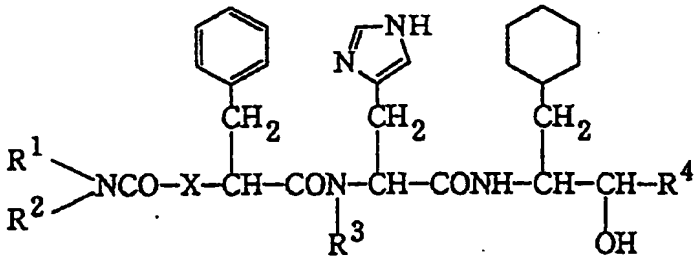
Example 9

Compound C	400 parts
Cetyl alcohol	400 parts
Lactose	105 parts
Crosslinked polyvinylpyrrolidone	80 parts
Magnesium stearate	15 parts

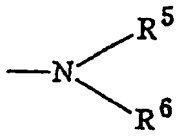
Tablets according to the above formula were manufactured by the conventional method.

CLAIMS

1. An oral pharmaceutical composition, which comprises an amino acid derivative of the general formula :



wherein R^1 is a lower alkyl group which may be substituted with a substituent selected from the group consisting of acyl, hydroxy, lower alkoxy, aryl, lower alkylthio and a group of the formula :



in which R^5 is hydrogen or an acyl group, and R^6 is hydrogen or a lower alkyl group,

R^2 is hydrogen or a lower alkyl group,

R^3 is hydrogen or a lower alkyl group,

R^4 is a lower alkyl group, and

X is O or NH,

or a salt thereof and one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

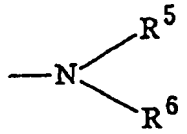
2. An oral pharmaceutical composition according to claim 1, which comprises an amino acid derivative of

claim 1 or a salt thereof and tartaric acid.

3. An oral pharmaceutical composition according to claim 1, which comprises an amino acid derivative of claim 1 or a salt thereof and cetyl alcohol.

4. An oral pharmaceutical composition according to claim 1, which comprises an amino acid derivative of claim 1 or a salt thereof and β-cyclodextrin.

5. An oral pharmaceutical composition according to claim 2, 3 or 4, in which an amino acid derivative is the one wherein R^1 is a lower alkyl group substituted with a group of the formula :



in which R^5 is hydrogen or morpholinocarbonyl, and R^6 is hydrogen or a lower alkyl group.

6. A process for preparing an oral pharmaceutical composition, which comprises blending an amino acid derivative of claim 1 or a salt thereof with one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

7. Use of an amino acid derivative of claim 1 or a salt thereof in the preparation of an oral pharmaceutical composition, together with one or more ingredient(s) selected from the group consisting of tartaric acid, citric acid, higher alcohol, cyclodextrin, sucrose ester of fatty acid and polyglycerin ester of fatty acid.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 94/00670

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/64 A61K47/10 A61K47/12 A61K47/14 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9050, Derwent Publications Ltd., London, GB; AN 90-370711 (50) cited in the application see abstract & JP,A,02 243 674 (FUJISAWA PHARM. KK) 27 September 1990 ---	1-7
A	EP,A,0 476 515 (FUJISAWA PHARMACEUTICAL CO.,LTD.) 25 March 1992 cited in the application see claims see page 13, line 35 - line 53 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 1994	12. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 9244, Derwent Publications Ltd., London, GB; AN 92-366167 (44) see abstract & WO,A,92 17456 (FUJISAWA PHARM. CO. LTD.) 15 October 1992 ---	1-7
P,A	WO,A,93 12796 (FUJISAWA PHARMACEUTICAL CO.,LTD.) 8 July 1993 see claims see page 11, line 29 - line 34 see page 12, line 1 - line 8 see examples -----	1-7

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	8379091	19-03-92
		CN-A-	1063691	19-08-92
		JP-A-	4279570	05-10-92
WO-A-9217456	15-10-92	NONE		
WO-A-9312796	08-07-93	AU-B-	3171293	28-07-93